Under the Microscope

Viruses and Diabetes: Is There Something Sweet About Hepatitis C Infection?

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The current classification of diabetes distinguishes type 1 from type 2 diabetes on the presumption that each disorder is caused by separate mechanisms. However, it is possible that similar genetic and environmental factors impact on the pathogenesis of both disorders. Patients with type 1, immune-mediated diabetes make antibodies to beta islet cell components, and it is thought that autoimmune damage to the beta islet cells of the pancreas eventually leads to hypoinsulinemia and hyperglycemia. In contrast, there is little evidence to suggest that immune destruction of islet cells leads to type 2 diabetes. The prevailing data indicate that abnormal glucose metabolism occurs in middle age as a result of peripheral insulin resistance associated with obesity and hyperinsulinemia. In fact, insulin resistance appears to be mediated by a recently discovered hormone called resistin (1). This hormone is secreted by adipocytes and suppresses insulin's ability to stimulate glucose uptake. As a result, patients with obesity produce more resistin, which leads to peripheral insulin resistance (1). In the 20% of patients with type 2 diabetes who are not overweight, other factors such as liver disease and specific medications contribute to the development of diabetes.

Even though some of the pathologic mechanisms that produce abnormal glucose metabolism and hyperglycemia are partially understood, the etiology of diabetes remains an enigma. Much like other idiopathic heterogeneous disorders, the development of diabetes appears to be influenced by a complex interaction of genetic, environmental, and dietary factors. Specific HLA haplotypes and genes associated with glucose metabolism have been linked to the development of type 1 and type 2 diabetes, respectively. Also, environmental factors such as viral infection have been shown to induce diabetes in animal models. Although no specific agents have been definitively linked to the development of disease in humans, reports have linked certain viruses with both type 1 and type 2 diabetes. Indeed, a growing number of epidemiologic studies suggest that hepatitis C virus (HCV) may be directly linked to the development of type 2 diabetes.

Viral Induction of Diabetes in Animal Models

Specific viral infections in mice have provided excellent models to investigate beta islet cell dysfunction. Three mechanisms have been proposed for the viral induction of diabetes, but they are not necessarily mutually exclusive. In the first instance, specific viruses have been found to inhibit the nonessential or "luxury" function of islet cells without damaging the pancreas. This phenomenon has been observed during both lymphocytic choriomeningitis virus and the Venezuelan encephalitis virus infection in mice. These agents are not directly cytopathic in the pancreas, but they infect beta islet cells and inhibit the normal biochemical function resulting in decreased insulin production (2). In contrast, the encephalomyocarditis virus exerts a direct cytopathic effect on islet cells in genetically susceptible mice (2). During infection with this agent, a more fulminating course of disease occurs as the virus

destroys both beta islet cells and the myocardium. It has also been proposed that viruses can act as triggers for autoantibody formation leading to immune destruction of the beta islet cells. For example, Reovirus 1 infection in mice results in autoantibody production to islet cells and their constituent proteins leading to abnormal glucose metabolism (2). These are but a few representative examples of virally induced diabetes.

Viral Infection and Type 1 Diabetes

In humans, several reports have hinted at an infectious trigger for type 1 diabetes, but no specific agent has been proven to cause disease. In infants, it has been reported that diabetes is more common in those suffering from congenital rubella as compared with the general population (3). Although it is likely that pancreatic damage occurs in utero, evidence for ongoing viral replication can be detected for up to 3 decades following congenital infection. Of further interest, rubella replicates in the tissues associated with vascular damage in patients with type 1 diabetes, such as the retina and kidneys (3). There are also data to link infection with Coxsackie virus and other enteroviruses to the development of type 1 diabetes. Seroconversion associated with rotavirus infection, for example, appears to correlate with increased levels of autoantibody levels and the development of hyperglycemia in children susceptible to the development of type 1 diabetes (4). Echovirus 9 is also associated with childhood diabetes but, unlike the Coxsackie viruses, this agent does not cause damage to beta islet cells or autoantibody formation (5). In contrast, Coxsackie virus infection is demonstrably cytopathic to beta islet cells in vitro and associated with autoantibody formation in vivo (5). Acute infection with Coxsackie B3 and B4 virus RNA has been linked to the development of type 1 diabetes and viral RNA persists in patients' serum (2, 6). The observation of regional amino acid homology between the P2-C proteins of Coxsackie B virus and the principal islet cell antigen, GAD, suggests that the virus induces an autoimmune response by the process of molecular mimicry (7). It has been suggested that an intracellular pathogen may gain a survival advantage by molecular mimicry of the host's cellular components when hiding from the immune system in an infected cell. On the other hand, sharing of immunodominant epitopes between pathogen and host may trigger an autoimmune response to cellular components in a susceptible host.

Two provocative reports suggesting the possibility of superantigen reactivity in patients with type 1 diabetes stimulated debate amongst clinicians and immunologists alike (8, 9). The implication of these studies was that a putative pathogen was directly stimulating T lymphocytes in an HLA unrestricted fashion to orchestrate the autoimmune destruction of beta islet cells. Conrad and colleagues reported that they had isolated a superantigen reactive endogenous retrovirus, IDDM $K_{1,2}$-22, that was specifically associated with the development of type 1 diabetes (8). There were several intrinsic problems with their data, however, and this hypothesis was contested by several groups interested in the viral induction of autoimmune disease (10). Specifically, we were unable to reproduce the data that infection with this endogenous retrovirus was specific to patients with type 1 diabetes (10). Indeed, endogenous retroviruses by their very nature have a markedly diminished capacity for replication and transmission because of restrictions imposed by their host. Generally, the expression of endogenous retroviral genes is silenced within the host's genome by point mutations, deletions, and methylation, and, even when viral proteins are synthesized, endogenous retroviruses often form noninfectious defective particles (11). In murine models, some endogenous retroviruses may cause infectious disease, but, in humans, none have been demonstrated to date, and the IDDM $K_{1,2}$-22 endogenous retrovirus hypothesis has been discarded.

Genome-wide mapping studies have revealed that genes within the major histocompatibility complex on chromosome 6 provide the greatest risk for developing type 1 diabetes. Although there is debate about which particular gene(s) within the region provide susceptibility, it is accepted that individuals with the extended haplotype DR4, DQA3, DQB3/2 have a 5- to 35-fold increased relative risk of developing type 1 diabetes (12). From an infectious disease standpoint, the most feasible model to explain the etiopathogenesis of type 1 diabetes is that patients with specific genetic predisposition become infected with a virus that usually does not result in diabetes. In individuals with the extended haplotype DR4, DQA3, DQB3/2, however, the virus may act as a trigger to stimulate the immune destruction of beta islet cells, possibly in connection with other unrecognized genetic and environmental factors. While there is no formal proof for this hypothesis, this model is consistent with observations from HLA studies in patients with viral hepatitis. For example, subjects with the extended haplotype A1, B8, DR3 are at increased risk of developing autoimmune liver disease, and HCV-positive patients with this haplotype are more likely to develop antinuclear antibodies than HCV infected patients without A1, B8, DR3 (13). A similar pattern is seen in patients with HCV infection and the DR4 haplotype. The combination of DR4 and HCV infection results in a 2- to 3-fold increased risk of developing extrahepatic or "immunologic" syndromes such as thyroid disease as compared with HCV-positive patients without the DR4 haplotype (13). Thus, specific HLA haplotypes may confer either susceptibility or protection to uncommon sequelae of viral infection. We will return to this model when considering the etiopathogenesis of type 2 diabetes and HCV infection, which also appears to be linked to a specific HLA haplotype.

Type 2 Diabetes and Liver Disease

Approximately 80% of patients with type 2 diabetes are obese and likely develop diabetes as a result of overproduction of the resistin hormone from adipocytes which leads to peripheral insulin resistance and hyperglycemia (1). It is likely that other mechanisms lead to abnormal glucose metabolism in the remaining 20% of type 2 diabetics who are not obese, such as patients with cirrhosis. Patients with liver disease are predisposed to diabetes for a variety of reasons, including HCV infection. Therefore, we should address the question whether HCV infection is associated with diabetes beyond the risk factors attributable to liver disease alone. This is not a simple task because both the cause of the liver disease, such as hemochromatosis, and the extent of liver disease can directly impact on glucose metabolism. There is also the reciprocal relationship to consider. Individuals with type 2 diabetes have an increased prevalence of cirrhosis, and Syndrome X patients with obesity, diabetes, and hypertriglyceridemia are more prone to the development of nonalcoholic steatohepatitis (NASH) and cirrhosis (14, 15).

A wide range (from 50% to 80%) of those with cirrhosis are reported to have impaired glucose tolerance, and approximately 20% develop type 2 diabetes mellitus (15-17). The disturbances in glucose metabolism are not restricted to cirrhotic patients; subjects with NASH, as well as patients with acute and chronic hepatitis, can also develop glucose intolerance (15, 18, 19). In the presence of parenchymal liver disease, hyperglycemia is associated with hyperinsulinemia secondary to reduced extraction of insulin from the enterohepatic circulation, but this is rarely associated with hypoglycemia as patients usually have peripheral insulin resistance in muscle tissue (18, 20, 21). Patients with liver disease may also develop impaired glucose tolerance because of medications, toxins, and concomitant pancreatic endocrine dysfunction. Corticosteroid and thiazide therapy are frequently prescribed to patients with hepatic disorders, while alcohol abuse is commonly associated with pancreatic and liver disease. Also, approximately 50% of patients presenting with hemochromatosis over the age of 45 are reported to have glucose intolerance due to the combined effects of hepatic and pancreatic disease (22)

HCV Infection and Type 2 Diabetes

The idea that HCV infection may be associated with diabetes became apparent during recruitment for antiviral clinical trials when a considerable proportion of patients with HCV infection had to be excluded because of diabetes. Since then, multiple epidemiologic studies have confirmed the suspicion that patients with HCV infection have a significantly higher prevalence of diabetes compared with other patients with liver disease (23-29). An association of HCV and diabetes has also been observed in cohorts of patients with diabetes (28, 30-32), thalassemia (33), and more recently in a large cross-sectional national survey (34). Immunogenetic studies have also hinted that an infectious process may be linked to type 2 diabetes in subjects with chronic liver disease. In a survey of two separate populations derived from liver transplant recipients at Ochsner Clinic and the Natioanl Institutes of Health Liver Transplant Database, the extended DR2, DR51, DQB6 haplotype was found to provide a 2.3 increased relative risk for the development of diabetes (35). Although the increase in susceptibility was modest, the similar finding in two independent databases is considered significant, and this study was the first to show an HLA association with type 2 diabetes. From these studies, it is tempting to use a similar model for both type 1 and type 2 diabetes and speculate that in some instances, type 2 diabetes may also occur as a result of viral infection in genetically predisposed individuals.

Cumulative reports from diverse geographic regions (Table 1) have shown a 2- to 10-fold increase in the prevalence of diabetes in patients with HCV infection compared with liver disease controls (23-29, 36). One study failed to support the association (36). Of note, strikingly similar observations were reported in the two largest retrospective studies incorporating more than 1000 patients with liver disease (26, 28). In a study conducted at the St. Louis Veterans Affairs Medical Center and the Ochsner Clinic, 21% of HCV-positive patients were found to have diabetes compared with 12% of patients with hepatitis B virus (HBV) infection (28). In an Italian cohort of cirrhotic patients, the prevalence of diabetes was found to be 24% in those with HCV and 9% in patients with HBV infection (26). In both studies, age and HCV infection were found to be independent variables associated with the development of diabetes.

Although individual reports addressed specific confounding issues, collectively the studies outlined in Table 1 have been criticized for the heterogeneity in the stage of liver disease as well as the lack of adequate matching of age, sex, body mass index, socioeconomic status, and race for each population (36). However, the trend for diabetes to occur in more homogeneous populations has also been reported in non-cirrhotic patients; for example, patients with thalassemia have a 4-fold increased risk of diabetes if they have HCV infection (33). Similar observations have been reported following liver transplantation. One year after liver transplantation, HCV-positive patients have a 4- to 8-fold increased prevalence of diabetes as compared with those with HBV infection or cholestatic liver disease, respectively (37).

The connection with diabetes and HCV infection has also been demonstrated in anti-HCV seroprevalence studies in cohorts with diabetes (Table 2). In a selected group of English type 2 diabetics with abnormal serum aminotransferases, 28% of patients of African origin, 12% of Caucasians, and 8% of Asians had evidence of HCV infection (30). At the Ochsner Clinic, 4.2% of consecutive patients from the diabetes clinic were found to be HCV antibody-positive

compared with 1.6% in the control group of patients undergoing thyroid scan (28). Other seroprevalence studies from Mediterranean countries noted a 5- to 10-fold increase in seroprevalence of HCV in diabetic patients (Table 2). These seroprevalence data should be interpreted with caution because of the lack of liver biopsy data to assess the severity of liver disease, ascertainment bias, and the difficulty in selecting adequate control groups. With regard to the latter, blood donors are a poor choice as control subjects as they have been specifically selected for low-risk behavior, exposure to parenteral blood products, and a lower prevalence of blood borne pathogens. Other questions have been raised concerning these HCV seroprevalence studies in patients with diabetes. It has been suggested that diabetic patients may have an additional risk of developing HCV infection because of increased exposure to medical interventions. Other criticisms of these studies include the insidious onset of both disorders, making it extremely difficult to demonstrate a temporal effect of HCV infection leading to diabetes. Despite these concerns, the increased prevalence of HCV infection is clearly demonstrable in diabetic populations, especially those with abnormal serum aminotransferases. Traditionally, abnormal hepatic biochemistry studies have been attributed to NASH in patients with type 2 diabetes, but at Ochsner Clinic one in five patients with diabetes and consistently abnormal serum aminotransferases had HCV infection, suggesting that this population should be screened for viral hepatitis (28).

The lingering doubts about the putative link of HCV infection with diabetes have now been addressed by a cross-sectional US study involving nearly 10 000 subjects. In this cohort, 8.4% had type 2 diabetes, 2.1% had HCV infection, and 0.5% had HBV infection (34). Multivariate analysis with matching of known risk factors revealed that HCV infection provided a greater than 3-fold increased risk of developing diabetes in individuals over 40 years old and 2-fold for those under 40 years old, whereas HBV infection had no discernable effect (34). None of the patients with type 1 diabetes had evidence of HCV infection, suggesting that the diagnosis of diabetes *per se* has little impact on the subsequent development of HCV. No liver biopsy data were available to assess the role of cirrhosis on the development of diabetes, but the mean platelet count was lower in HCV-infected individuals with diabetes compared with subjects without type 2 diabetes. There was no indication that diabetes was occurring specifically in patients with severe liver dysfunction, as markers for end-stage liver disease such as increased bilirubin or diminished albumin did not differ in the diabetic and nondiabetic cohorts with HCV infection (34). Unfortunately, this study provided no data on a temporal relationship for the onset of each disease or the use of intravenous drugs.

Table 1. Prevalence of diabetes in patients with chronic liver disease.

Diabetes		Sample size	Population	Reference
HCV	Liver disease controls			
33%	12%	133	Non-cirrhotic, US	(27)
21%	12%	1117	Liver disease, US	(28)
25%	11%	814	Liver disease, Egypt	(24)
39%	3%	168	Liver disease, Israel	(25)
23%	21%	358	Liver disease, Italy	(36)
50%	9%	100	Cirrhotic, UK	(23)
23%	9.4%	1332	Cirrhotic, Italy	(26)
19%	2%	161	Cirrhotic, US	(29)

Table 2. Prevalence of anti-HCV in the serum of patients with diabetes and control populations.

Sample size	Liver function tests	HCV		Reference
		Diabetes	Control Population	
100	Normal	1%	0.5% blood donors, UK	(30)
100	Abnormal	15%		
342	Normal	2.3%	1.6% thyroid scan, US	(28)
218	Abnormal	7.3%		
124	Normal	4%	2.5% blood donors, Spain	(32)
51	Abnormal	25%		
100	Unknown	8%	0.7% blood donors, Turkey	(31)

The notion that HCV infection can mediate type 2 diabetes appears credible, but the viral mechanisms that cause glucose intolerance require further investigation. It is clear that liver disease plays some role in glucose intolerance, but, if the same model for type 1 diabetes is used as a basis for viral induction of type 2 diabetes, there are limited data to suggest that HCV causes pancreatic damage. Diabetes in HCV-positive patients is not specifically associated with autoantibody production, so autoimmune destruction of the pancreas does not appear to be an important mechanism (24, 28). There is some evidence that HCV-positive diabetics have beta islet cell dysfunction with decreased C-peptide levels and limited acute insulin responses (26, 38, 39). Even though HCV can replicate in the pancreas (40), there are no adequate animal or in vitro models to test the hypothesis that HCV directly damages beta islet cells or disturbs their synthetic function. However, improvements in glucose metabolism have been observed following antiviral treatment (39). Prospective longitudinal studies assessing endocrine responses to antiviral therapy are needed to provide further insight into the pathogenesis of viral induction of diabetes and stem the epidemic of HCV infection and diabetes.

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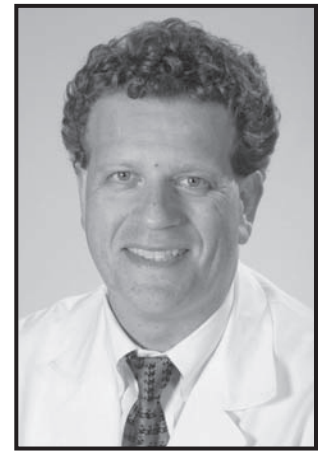

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